b.) Remarks

Claims 16 and 42 have been amended in order to recite the present invention with the specificity required by statute and claims 19 and 43 are amended in conformity therewith. Claims 49 and 50 have been added to recite further preferred embodiments of the present invention. Claim 35 is amended to correct its dependency.

The subject matter of the amendment may be found in the specification as filed, *inter alia*, at Examples 1 (page 17, lines 10-13), 2 (page 18, lines 7-8) and 3 (page 18, lines 12-13). Accordingly, no new matter has been added.

Claims 16, 19, 20, 35 and 42-44 are rejected under 35 U.S.C §103(a) as being obvious over EP 0 850,646 by itself or Woodle '633 by itself, or Woodle '633 or '566 or Allen (U.S. Patent No. 4,920,016) in combination with EP '646.

In support of the rejection, the Examiner states that one of ordinary skill in the art would prepare liposomes having the desired diameter based on EP '646 or Woodle '633.

EP '646 teaches the inhibition of leakage of the indolocarbazole derivative from liposomes in phosphate buffer. In contrast, the present invention achieves inhibition of leakage of these materials in biological components, e.g. blood and the like. (As discussed later, EP 646 is alone in relating to leakage. The other prior art relates to other disparate performance parameters.)

By way of background, as the Examiner is aware, the liposomes of the present invention are liposomes with an average particle size of 120 to 500 nm, the lipid of which is now (i) hydrogenated soybean phosphatidylcholine or (ii) mixed lipids of

hydrogenated soybean phosphatidylcholine and polyethylene glycol-modified distearoyl phosphoethanolamine.

As shown in the Table 1 of the present specification, the liposomes of the present invention far more strongly inhibit the leakage of the indolocarbazole derivative from liposomes in biological components when compared to liposomes having an average particle size of 109 nm (see Comparative Example 1), or when compared to liposomes comprising egg phosphatidylcholine or dipalmitoyl phosphatidylcholine (see Comparative Examples 2 and 3, respectively). Applicants also showed that liposomes having an average particle size of 98 nm and liposomes comprising cholesterol easily leak the indolocarbazole derivative from the liposome in biological components (see Comparative Examples 6 and 4, respectively, in the Declaration filed September 23, 2005).

Therefore, Applicants maintain it would have been unobvious to prepare liposome having an average particle sizes are 120 to 500 nm and comprising hydrogenated soybean phosphatidylcholine and/or mixed lipids of hydrogenated soybean phosphatidylcholine.

In response, the Examiner points out that, first, the data presented is not commensurate with the term 'polyethylene glycol modified phospholipid'. Second, the Examiner states the data presented is not commensurate with the sizes of liposomes recited in claims. Third, the Examiner states EP '646 does teach inhibiting the leakage of the indolocarbazole derivative from liposome. Fourth, the Examiner states Applicants' conclusions are impermissibly based on a single experiment. These points are addressed below, in turn.

First, Applicants have amended the term 'polyethylene glycol-modified phospholipid' to 'polyethylene glycol-modified distearoyl phosphoethanolamine'.

Second, Table 1 in the present specification shows that liposome having an average particle sizes of 186, 130, 136 and 180 nm (see Examples 1 to 4) all exhibit superior inhibition of leakage of indolocarbazole derivative in human AGP-containing rat plasma.

In this regard, as explained in the previously filed Declaration (see Figure 1), inhibition of leakage of the indolocarbazole derivative from said liposome depended on the particle size and the inhibition ratio of more than 50% was observed on the liposomes having the particle size of more than 120 nm. That is to say, the larger size of the particle size results in excessive inhibition of liposomal leakage[1].

Therefore, the data presented in the present application is commensurate with the scope of the claims.

Third, as discussed above, EP '646 only teaches the inhibition of leakage of the indolocarbazole derivative from liposomes in phosphate buffer and not in biological components. Accordingly, EP 646 neither teaches nor suggests the effective result of Applicants' liposomes in biological components. Indeed, as shown by the evidence already of record, EP '646 does not achieve such dramatically improved performance. That is, of course, the hallmark of unobviousness.

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[1] On the other hand, it is well-known that liposomes having the particle size of more than 500 nm shows rapid clearance from bloodstream by being distributed to tissues *in vivo* (see, col. 3, lines 6-13 in Woodle 633, and Fig. 5 in Chem. Pharm. Bull., 41, (1993) 599-604).

In regard to the fourth point, Applicants' conclusions (that there is a definite correlation between the particle size of a liposome and the leakage of the indolocarbazole derivative) are based on results obtained by using thirteen different particle sizes of liposomes.

In further support of the rejection, the Examiner states that one of ordinary skill in the art could encapsulate any desired drug within the liposomes based on the guidance provided by Woodle or Allen, especially in view of EP '646. As discussed above, however, Woodle '633, '556 and Allen only teach the retention of their liposome in blood, but does not teach or suggest inhibition of leakage of any liposomes in the presence of biological product. It is well-understood by those of ordinary skill in the art that these are disparate, unrelated performance criteria.

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition. Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claims 16, 19, 20, 35, 42-44, 49 and 50 remain presented for continued prosecution.

Applicant's undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

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